A REVIEW OF ADULT TONSIL HISTOPATHOLOGY AND THE EFFECT OF CONCOMITANT HUMAN IMMUNODEFICIENCY VIRUS INFECTION

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DECLARATION

I, Ridwaan Essa declare that this thesis is my own work. It is being submitted for the degree of Master of Medicine in Otorhinolaryngology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

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Ridwaan Essa

Signed at Charlotte Maxeke Johannesburg Academic Hospital on this day 5 December 2017

DEDICATION

I dedicate this work to my wife and child (Shahista, Muhammed), parents (Suleiman, Najumunnisia), and siblings. Thank you all for your patience.

ABSTRACT

Objective:

To review the histopathological diagnoses of palatine tonsil diseases and to compare the incidence of malignancy in HIV infected and HIV uninfected patients.

Methods:

This study is a retrospective record review over the period 1 July 2005 to 30 June 2015. The patients were recruited from the Otorhinolaryngology departments at the Chris Hani Baragwanath Academic Hospital, Charlotte Maxeke Johannesburg Academic Hospital and Helen Joseph Hospital. Records were collected from the National Health Care Laboratory database of patients above 18 years of age.

Results:

The histology results of 319 patients were obtained. Reactive lymphoid hyperplasia was present in the vast majority (77.3%). Fourteen patients had underlying malignancies.

There were 86 patients who were HIV infected and 74 were HIV uninfected. The rest of the patients' HIV status was not known. Eight malignancies (9.3%) were discovered in the HIV infected patients and 6 malignancies (8.1%) were discovered in the HIV uninfected patients.

There was no statistically significant difference in the incidence of malignancies between the HIV infected and uninfected groups.

Conclusion:

The majority of patients undergoing tonsillectomy had an underlying benign condition.

HIV status does not appear to be a risk factor for tonsil malignancies other than Kaposi's sarcoma.

ACKNOWLEDGMENTS

I would like to afford my gratitude towards Dr K Hari, for the time we spent together working long hours in preparation for this MMED, her guidance was greatly appreciated. I would also like to thank Dr S Motakef and Prof PC Modi for the insight and direction they afforded me.

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LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
ART	Anti-retroviral therapy
EBV	Ebstein Barr Virus
CD4	Cluster of differentiation 4
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
HHV8	Human Herpes Virus 8
HJH	Helen Joseph Hospital
HIV	Human Immunodeficiency virus
HPV	Human Papilloma Virus
KS	Kaposi's sarcoma (KS)
NADCs	Non-AIDS defining cancers
NHL	Non-Hodgkins lymphoma
Rb	Retinoblastoma
SCC	Squamous cell carcinoma
TB	Mycobacterium Tuberculosis
USA	United States of America
WITS University	University of the Witwatersrand

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CHAPTER 1

INTRODUCTION

In resource rich centres, histopathology assessments are performed routinely on tonsillectomy patients.[1] This routine histopathology may reveal unexpected malignant lesions. The incidence of unexpected malignant lesions is extremely rare (0.015%)[1] but early diagnosis in these instances could lead to timely treatment and an improved prognosis. The merits of routine tonsillar histopathology in poorly resourced centres have been questioned.[2] The staff at the Department of Otorhinolaryngology at the University of the Witwatersrand (WITS University) request histopathology for suspicious lesions based on the attending doctor's evaluation.

It has been documented that Human Immunodeficiency Virus (HIV) infection increases the risk of malignant lesions.[1, 3] There is limited published data on the specific risks of malignant tonsillar lesions in Johannesburg. This study aims to assess whether there is a benefit to performing routine histopathology on tonsillar specimens in HIV infected and HIV uninfected patients.

We will review the data of tonsillar specimens sent for histopathology from the three hospitals affiliated to WITS University namely Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Baragwaneth Academic Hospital (CHBAH) and Helen Joseph Hospital (HJH).

1.1 Background

Tonsillectomies are common surgical procedures performed by Otorhinolaryngologists.[1] The majority of these are routine procedures.

The indications include:

- Hypertrophy secondary to inflammatory conditions
    - Allergies
    - Infections
    - Chemical irritations related to post-nasal drip
    - Reflux disease
- Obstructive Sleep Apnoea
- Snoring[4]

Adult tonsillectomies may have a more significant aspect to it. Most are performed due to recurrent acute inflammatory disease but some may be due to more serious diseases including:

- Chronic granulomatous diseases
- Neoplasms
    - Benign
    - Malignant
        - Squamous Cell Carcinoma (SCC)

          The incidence of SCC has increased in the recent past. This may be attributed to the increase in infection with Human Papilloma Virus (HPV).[5]

          Factors associated with SCC include[4]
            - Alcohol consumption
            - Smoking
            - Increasing age
        - Lymphoma (more common in children) [1-3]

Beaty et al in 1998 identified certain features which were statistically significant in patients with tonsillar malignancy

- High risk factors for malignancy
    - History of cancer
    - Tonsillar asymmetry
    - Tonsil firmness
    - Visible lesions
    - Concomitant neck adenopathy
    - Unexpected weight loss
    - Constitutional symptoms (fatigue; night sweats; fever; anorexia)[6]

Recent evidence suggests that immunodeficiency should be considered an additional risk factor.[7]

In resource rich centres, litigation and patient demand drive requests for routine histopathology. The rationale behind routine histopathlogy has been questioned especially in poor areas where costs are a driving force.[2]

The initial recommendation for the performance of routine histopathological examination of tonsillar specimens came in 1939 by Starry who in a small series found 2 malignancies.[8] This practice was only questioned in 1964 by Weibel.[8] He examined 3627 tonsillar specimens and did not detect malignancy in any of them. He suggested that routine histological analysis should only be performed in patients >40 years.[8] In recent times numerous studies have also brought these practices into question.[1,2,8,15,16]

A recent systematic review by Rokkjaer et al (12 studies including 6434 patients) concluded that there is inadequate proof for routine histological examinations from patients who do not exhibit high risk features.[8]

Two studies from Africa including a paediatric study from South Africa were included in this review.[1,9] Adoga et al evaluated the histology of 61 tonsillectomy patients (adults and children) in Nigeria. They concluded that histological examination of tonsillar specimens was indicated in the presence of the risk factors listed above and should not be performed routinely.[9]

Van Lierop and Prescott concluded from their analysis of 344 specimens that routine pathological examination of tonsillar specimens is not indicated in South African children. They suggested further criteria to be considered when requesting histopathology studies of tonsillar specimens:

- Positive tuberculosis contact at home
- HIV infection
- Rapid tonsillar enlargement[1]

In view of the limited data in our setting, especially in the adult population where the prevalence of HIV infection is high (18% in the adult population) [10], we set out to determine whether routine tonsillar histological studies were indicated, especially in HIV infected patients.

1.2 Gross Anatomy

The palatine tonsils, pharyngeal tonsils and lingual tonsils are collectively known as Waldeyer's ring. See Figure 1.1 below. This lymphoid tissue is found at the entrance of the upper aero-digestive tract, being the first primary lymphoid tissue to be exposed to aero-digestive tract antigens resulting in an immune response. The palatine tonsils are paired oval masses located on the lateral walls of the oropharynx.[11] They are bounded by the anterior tonsillar pillars with its underlying palatoglossal muscle anteriorly and the posterior tonsillar pillars with its underlying palatopharyngeus and superior constrictor muscles posteriorly and laterally.[4, 11]

The blood supply to the tonsils is from the branches of the internal maxillary artery, ascending pharyngeal artery, facial artery and lingual artery.[11] Venous blood drainage is through a peritonsillar plexus. The plexus drains into the lingual and pharyngeal veins. This then drains into the internal jugular vein.[4, 11]

The sensory innervation is from the glossopharyngeal nerve (special sensory and general sensory) and some branches of the lesser palatine nerve (general sensory) via the sphenopalatine ganglion.[4, 11]

The palatine tonsils do not possess afferent lymphatics. However, efferent lymphatics drain directly to the jugulo-digastric lymph nodes and to the upper deep cervical chain of lymph nodes of the anterior triangle of the neck.[4, 11]

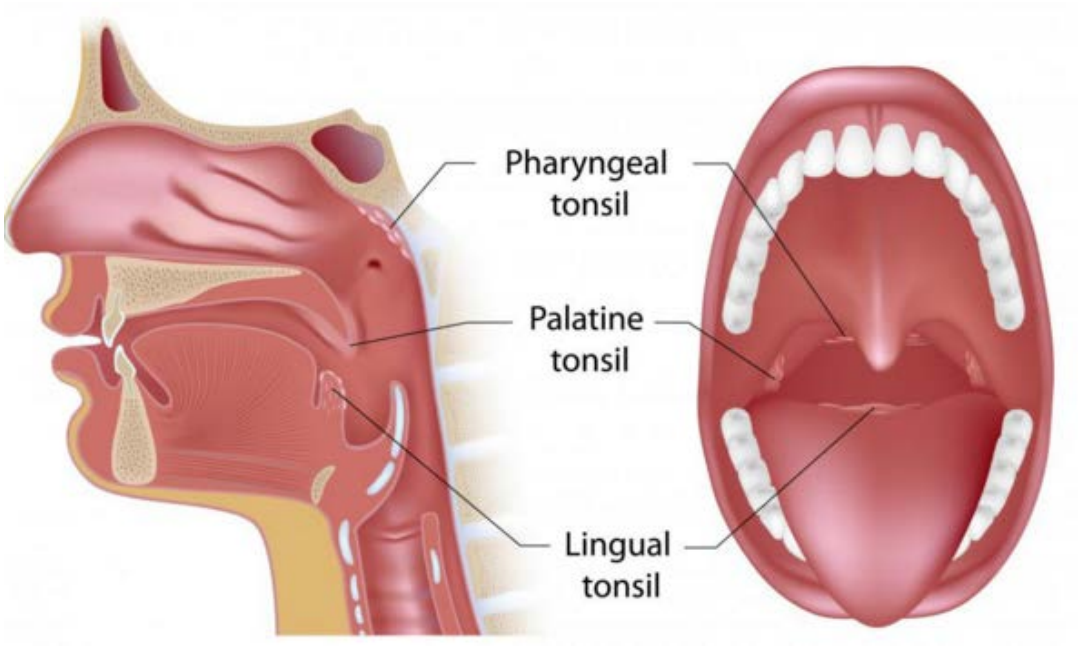

Fig 1.1Basic illustration of the Waldeyers ring[12]

1.3 The Microanatomy / Histology Of Normal Tonsillar Tissue

The palatine tonsil consists of lymphoid tissue and a connective tissue frame-work.[11] See Figure 1.2 below. The surface of the tonsil is covered with non-keratinizing stratified squamous epithelium. Epithelial lined tonsillar crypts penetrate nearly the entire tissue. This lining epithelium with its stroma are specialised in antigen processing. The crypts serve to increase surface area.[4, 11]

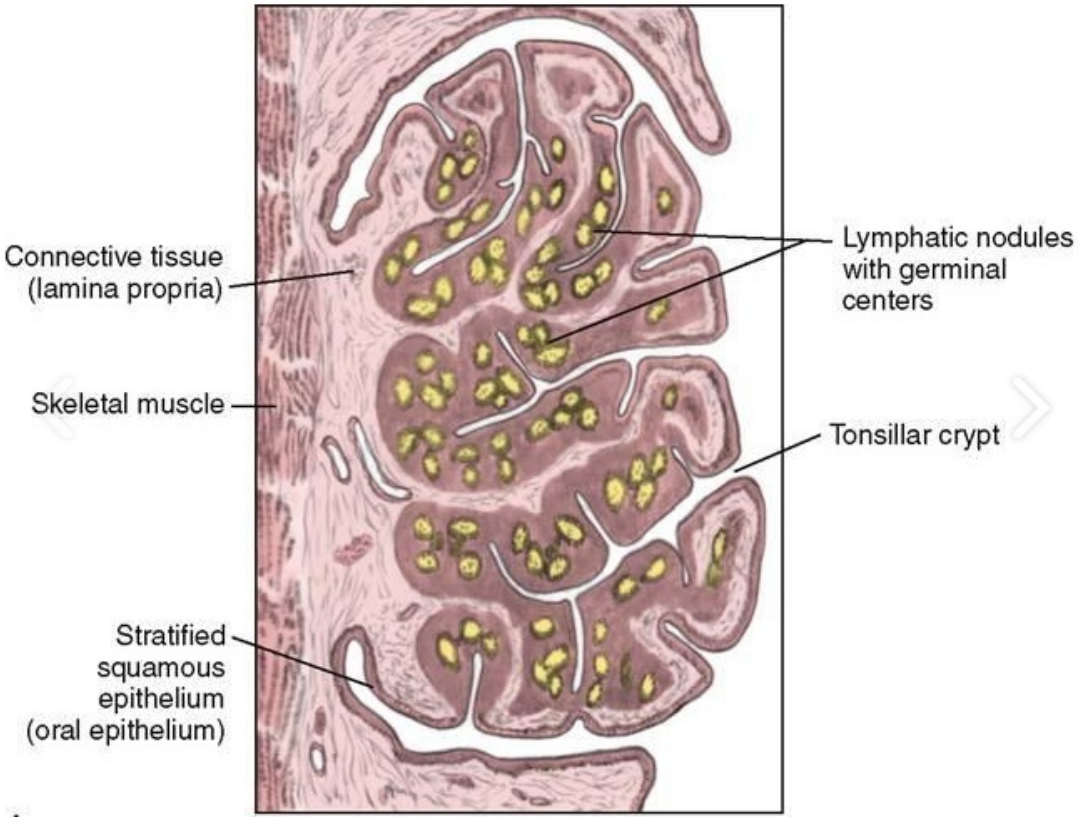

Figure 1.2 Microanatomy of palatine tonsils[13]

1.4 Function Of The Palatine Tonsils

They play an important role in surveillance and response to infection in the upper aero digestive tract. They are located in a prime position to act as secondary lymphoid tissue to foreign organisms introduced to the oral cavity. The antigen processing is initiated in the crypt epithelium and it then travels to the lymphoid follicles of the palatine tonsils, producing mature B and T lymphocytes.[4,11]

CHAPTER 2

LITERATURE REVIEW

2.1. Incidence Of Malignant Lesions In Tonsillar Tissue

Table 2.1: Incidence of Non-Benign Tonsillar Lesions

Authors	No. of Patients	Age Group	Malignant lesions (%)
Rokkjaeret al (2014)[8]	72,322	All ages	0.02 (unsuspected malignancy)
	6434	Adults	0.05 (unsuspected malignancy)
Hajiioannou et al (2014)[2]	823	All ages	0 (unsuspected malignancy)
Randall et al (2007)[15]	54,901	All ages	0.011 (unsuspected malignancy) 0,09 (suspected and unsuspected)
Courville et al (2011)[11]	1997	Adults	0 (unsuspected malignancy) 4 (suspected and unsuspected) * 30% of patients who had a suspicious lesion had a malignancy

Suspected Malignancy refers to the presence of the following risk factors:

- History of cancer
- Tonsillar asymmetry
- Tonsil firmness
- Visible lesions
- Concomitant neck adenopathy
- Unexpected weight loss
- Constitutional symptoms[8]

The world-wide incidence of tonsillar tumours is rare, accounting for only 0.05% of the tonsillectomy population.[5, 14.] The most common malignancies of the palatine tonsil in adults are squamous cell carcinoma (SCC) and lymphoma[5, 8, 14]

Rokkjaer et al (2014) performed a systematic literature review to determine the prevalence of unsuspected tonsillar malignancy. Their review included 72,322 patients of all ages and showed that only 0.02% of the patients had unsuspected malignancy. From extrapolation of the data only 0.05% of adults (above 18 years) who had a tonsillectomy, were found to have a non-benign lesion. They surmised that the high costs of testing all patients versus the opportunity of prolonging life by discovering an early lesion still needed further study.[8]

In 2014 Hajiioannou et al conducted a retrospective review of 823 tonsillectomies. They included patients of all age ranges and found no unsuspected malignancies. Thirty percent of the patients reviewed were above 18 years of age. They concluded that histopathological examination of tonsillectomy specimens is only indicated in patients with previously described clinical criteria that were suggestive of underlying malignancy.[2]

Randall et al (2007) performed a systemic review of 20 studies of tonsillectomy histology. Some of the studies in the review included adenoidectomy histology. There were 54,901 patients that had undergone tonsillectomies (ages ranged from 2 to 72years). Only 0.01% of

the patients had an unsuspected malignant lesion. None of the patients with an unsuspected malignancy were adult. There were 2138 adult patients, 25 (1.2%) of whom had a malignancy. Crucially all these adult patients had at least one risk factor for a suspected malignancy.[15]

Courville et al (2011) performed a retrospective review of 1997 adult tonsillectomy histology specimens performed over a 45 month period. In their study, 75 patients (3.7%) had squamous cell carcinoma; 11 (0.5%) had a lymphoproliferative disorder and 1 patient (0.05%) had a muco-epidermoid lesion. These were all suspected malignancies as the patient had identifiable risk factor/s. No unsuspected malignancy was found. Malignant lesions were detected in 30% of patients with "suspected malignancy". The authors concluded that the indication for sending a specimen for histology in an unsuspected case should be institution based as no study on the consequences of missing an undetected tonsil malignancy has been done[16].

Few studies have documented the effect of HIV infection on tonsillar histology. One Nigerian study by Adoga, et al (2011) reviewed 61 patients. The cohort comprised 35 children and 26 adults. They did not comment on the number of patients with HIV infection; although they did detect lymphoma in an adult patient with HIV. They concluded that a request for histopathology on tonsillectomy specimens should be based on the presence of established risk factors with consideration of the cost to patients and to spare histopathological resources.[9]

A South African Study, by Lierop et al (2009), evaluated the impact of HIV on the incidence of adeno-tonsillar lesions in the paediatric population. Of the 172 patients evaluated in their study, 50% were HIV positive. They detected only one case of lymphoma. That patient was

HIV negative. They concluded that, given the high cost of pathological examinations, routine pathology would not be cost effective, even with consideration of medico-legal prosecution.[1]

2.2 Human Papilloma Virus And Malignant Tonsillar Lesions

The Human Papilloma Virus (HPV) is a small non enveloped DNA virus. These viruses are found in the basal layer of epithelial cells present, where they replicate via a break in the skin or mucosa.[17] An increase in the incidence of oropharyngeal squamous cell carcinoma has been documented worldwide; this is associated with the new recognition of human papilloma virus as a cause of SCC [5, 17]. In the United States of America (USA) the incidence of oropharyngeal cancer has increased from 3.5 to 4.5 per hundred thousand between 2000 and 2010 indicating that the rate of tonsillar tumours increased 2-3% on a yearly basis.[5] This pattern follows a recent change in sexual behaviours.[17,18] Patients with HPV head and neck malignancy are usually younger and have an equal distribution between men and women, these patients do not have a history of smoking or alcohol intake in contrast to smoking related cancers.[17,18]

HPV is most commonly associated with the oropharynx in head and neck lesions possibly due the similarity of the mucosa to that of the uterine cervix, specifically the crypts of the tonsils.[17] HPV is transmitted peri-natally during vaginal births, sexually and via direct contact. HPV 16 and 18 are considered high risk subtypes implicated in malignancy. HPV 16 has been found in 90% of HPV positive cases of malignant head and neck tumours.[17, 18]

The mechanism of HPV carcinogenesis is via the encoding of HPV E6 and E7 oncogenes which bind to and inactivate tumour suppressors' p53 and retinoblastoma tumour suppressor protein(Rb) respectively. This results in uncontrolled cell growth.[17, 18]

It has been demonstrated that patients with oropharyngeal squamous cell carcinoma secondary to HPV have a better prognosis than patients in whom the malignancy is presumed to be secondary to smoking. Currently quadravalent and bivalent HPV vaccines appear to be

reducing the occurrence of cervical malignancy, this effect may extend into oropharyngeal cancers but definitive trials are pending.[17, 18]

2.3 HIV and the Palatine Tonsil

The palatine tonsils play an important role in immunologic surveillance and resistance to infection in the upper aero digestive tract.See Figure 2.1 below. Palatine tonsils taken from individuals infected with HIV-1 have shown infected lymphocytes localized to the surface of the tonsillar crypt epithelium. Thus HIV may replicate rapidly at this site due to the numerous T-cells and dendritic cellspresent. HIV is rarely transferred through the oral cavity and oropharynx as long as the mucosa is intact as demonstrated by a laboratory experiment whereby minimal transfer of HIV was found after human tonsillar tissue was bathed in HIV semen with an intact mucosa.[19]

The effects of HIV on the palatine tonsil are as follows:

- Acute phase of HIV infection
    - The secondary lymphoid organs show follicular hyperplasia and proliferation of vascular stroma.
    - The germinal centres of these organs are important reservoirs of free virus.
- Disease progression
    - Germinal centres lyse and involute.
    - Cluster of Differentiation (CD4) T cells deplete.
    - Increased collagen deposition in the palatine tonsils.
    - Greater depletion of CD4+ T cells.[20]

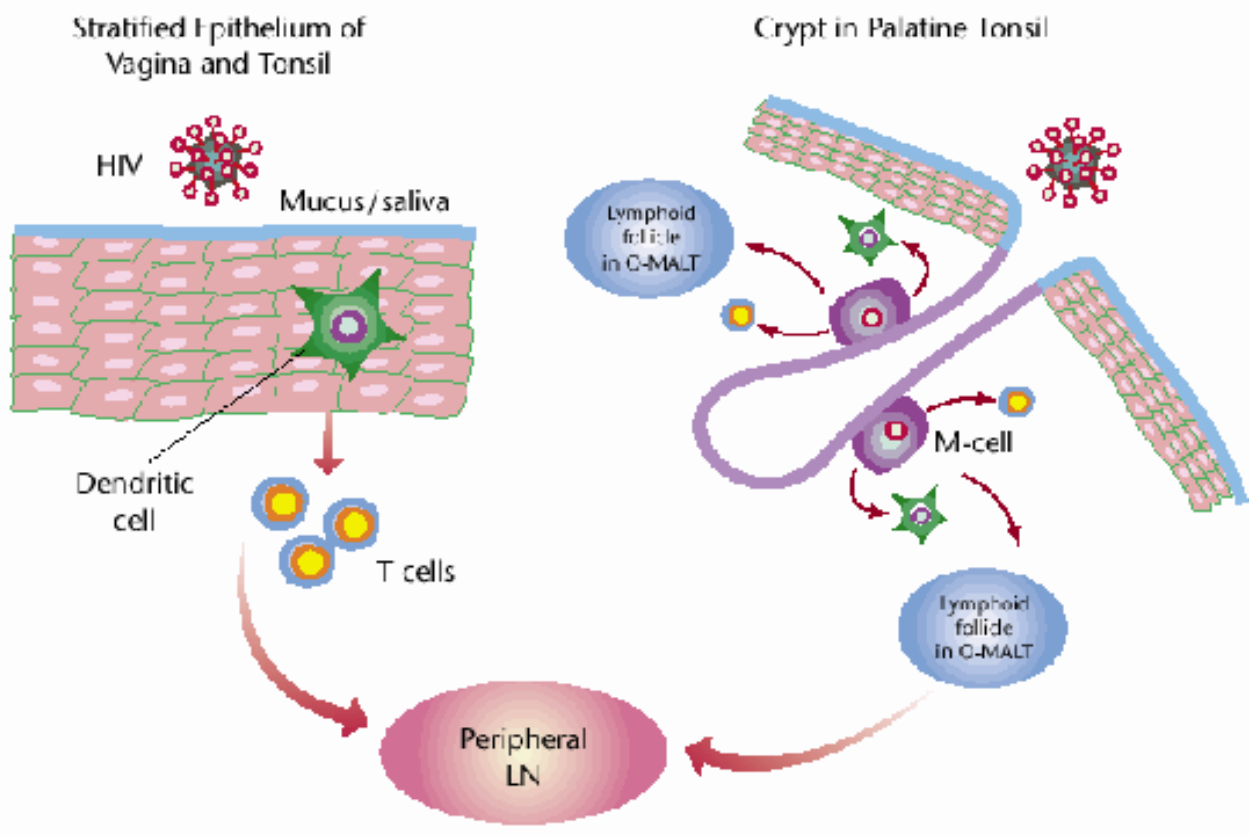

Fig 2.1 Infection of tonsil by HIV[21]

2.4 HIV And Benign Oral Lesions

The following oral lesions are more common in individuals with underlying HIV infection:

- Tuberculosis (TB)
- Syphillis
- Candidiasis
- Hairy leukoplakia
- Aphthous ulcers
- Herpes simplex viral infections[3]

HIV infection has been shown to result in a 30 times greater risk of developing tuberculosis.[1] TB of the tonsils however is a rare entity, with only a few cases having been reported. It is thought that saliva has a protective effect, making upper respiratory tract infections rare.[23] TB involving the tonsil is very rare because of pasteurization which destroys the bovine strain of tuberculosis contained in cow's milk. The tonsils are exposed in the oral cavity but due to the antiseptic nature of saliva, the presence of commensal organisms and the stratified squamous epithelium in the oral cavity; infection of the tonsil rarely occurs. Patients can present with caseating material from the tonsil mimicking a malignancy.[22, 23]

Syphilis is also a rare presentation of tonsillitis occurring with ulcers involving the tonsils. Patients may not describe genital symptoms and the diagnosis is occasionally discovered un-expectantly via biopsy.[24]

Actinomycosis is a subacute-to-chronic bacterial infection caused by filamentous, anaerobic-to-microaerophilic bacteria in the oral cavity.[2] They are commensals which can cause recurrent tonsillitis. Actinomycosis can be exacerbated in immune compromised patients and those with poor dental hygiene.[25] It is important to diagnose this organism as symptomatic patients may require long term antibiotics.[25, 26]

2.5 HIV And Malignant Lesions

HIV infection is associated with an increased risk of a range of malignancies:

- Acquired Immunodeficiency Syndrome (AIDS)-defining (virus related)
    - Kaposi sarcoma (KS)
    - Non-Hodgkins lymphoma (NHL)
    - Cervical cancer
- Non–AIDS defining carcinomas (NADC)
    - Lung
    - Liver
    - Anal
    - Tonsillar[3]

In the case of tonsillar malignancies, co-infection with HPV was thought to be responsible for the increase but HIV in itself may play a role.[3]

KS is a frequently reported mesenchymal neoplasm characterized by neoangiogenesis, and endothelial-derived, spindle shaped tumour cells in HIV infected people and it is caused by Human Herpes Virus 8(HHV8). KS is usually isolated to the skin and oral mucosa although it may also occur in the lungs, the liver, the stomach, the bowel and lymph nodes. It has been described in specific mucosal sites including the pharynx, larynx, nasal cavity, oral cavity and the palatine tonsil.[27]

Lymphomas are the most common malignancy in HIV-infected individuals. They represent more than 50% of AIDS related malignancies. HIV associated lymphomas are usually:

- High grade
- Clinically advanced at presentation
- Associated with extra nodal disease

Common NHL occurring with HIV are diffuse large B cell lymphoma and Burkitt's lymphoma. Hodgkins lymphoma does occur, but not as commonly as NHL.[7]

Mitsuyasu in 2013 reviewed the cancer and HIV matched registries from the USA and documented his findings (see graphs below). Significant findings were an increased incidence of liver, anal and lung malignancies in HIV infected patients. Hodgkins lymphoma was also found in larger numbers in older HIV infected patients.[28]

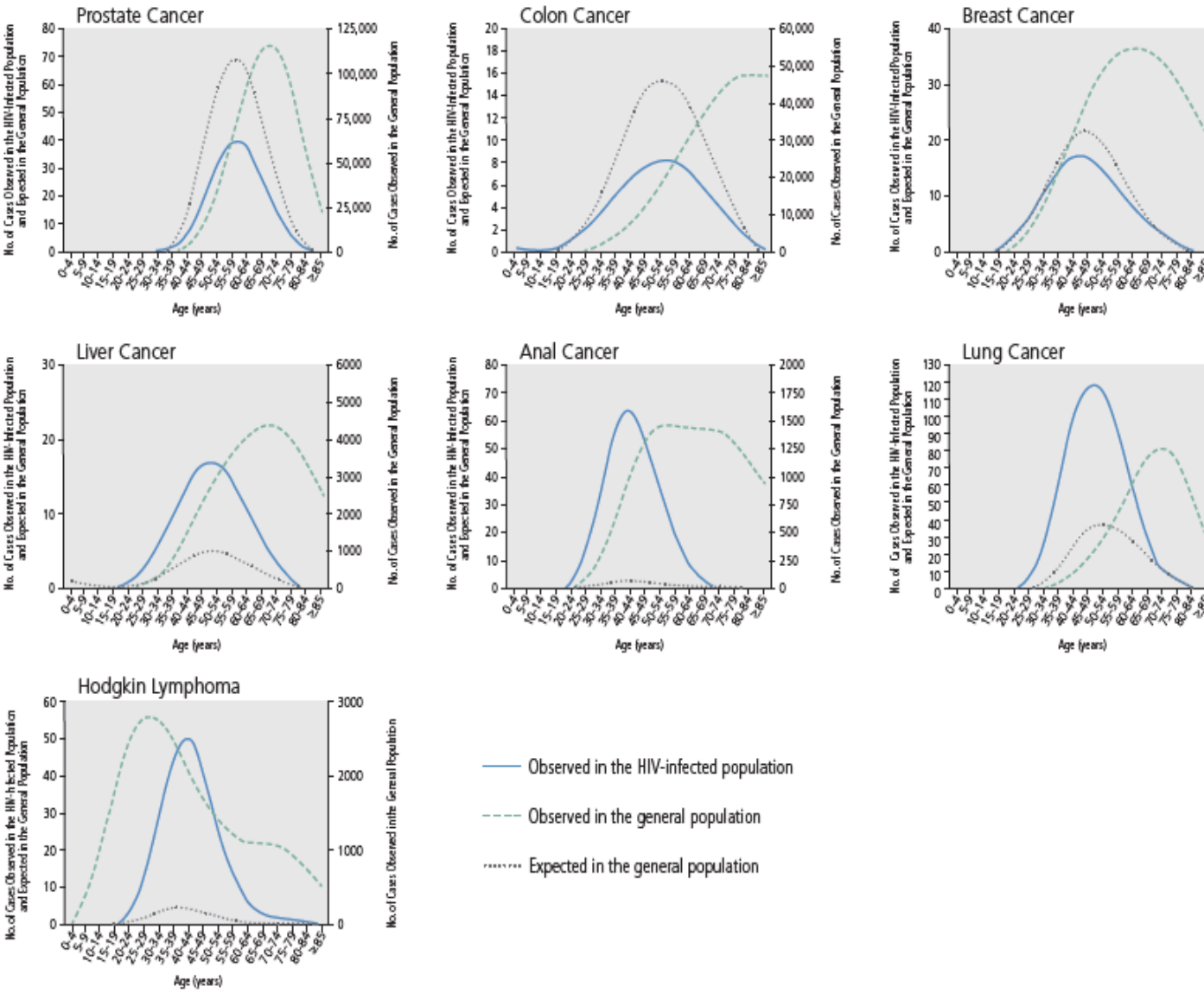

Figure 2.2 Graph depicting differences of NADC in HIV infected and uninfected individuals[28]

It has been shown that for NADC the CD4 count does not appear to play a singular role in carcinoma development.[3, 28] It is thought that co infection with certain viruses resulted in an increased incidence of malignancy. The viruses implicated are HPV, EBV (Epstein Barr Virus), Hepatitis Band C and HHV 8.[28] There is also a growing body of evidence that HIV has a direct effect on oncogenes and inactivates tumour suppressor genes; it may even cause more susceptibility to the effects of the co-existing viral infections. It has been shown that cells involved in the immune system of HIV positive patients have a shortening of the telomeres.[7] This may indicate that HIV positive patients have a more rapid rate of immunologic aging predisposing to malignancy[7, 28].

Chapter 3

MATERIALS & METHODS

3.1 Hypothesis

Routine histopathology of tonsillectomy specimens is unwarranted in the absence of identified risk factors.

South Africa has a high prevalence of HIV disease. This could result in an associated increase in the number of patients with specific HIV-related pathology of the palatine tonsils (specifically malignant lesions) compared to the HIV-uninfected.

3.2 Aims And Objectives

- To review the histopathological diagnoses of routine palatine tonsil diseases as seen in the Department of Otorhinolaryngology at the academic hospitals affiliated to WITS University.
- To compare the histological findings in HIV infected and HIV uninfected patients.

3.3 Study Design

This study is a retrospective record review.

- Study period

  A 10-year period from 1 July 2005 to 30June 2015.

3.4 Study Location

The study was conducted in the clinical units of University of the Witwatersrand's Department of Otorhinolaryngology at the following hospitals:

- CHBAH
- CMJAH
- HJH

3.5 Study Population

The study population included all patients older than 18 years of age, who had a tonsillectomy performed with a histological analysis over the defined study period.

3.5.1 Inclusion criteria

- All adult patients who had a tonsillectomy performed and for whom histopathological results were available on the National Health Laboratory Services (NHLS) database.
- Patients who had been clinically assessed by members of the Department of Otorhinolaryngology.

3.5.2 Exclusion criteria

- Inadequate data

3.6 Data Collection

Patients were identified from the ENT Operating Theatre Register, This information was used to obtain histopathology and blood results from the NHLS database.

3.7 Data Recorded included (see Appendix B):

- Hospital registration number
- Age
- Date of surgery
- Histology result
- HIV results
- CD4 count

3.8 Data Analysis And Presentation

- See results chapter

3.9 Ethics Committee Approval (see Appendix A)

- Ethics approval was obtained in March 2016.

3.10 Limitations

- Limited number of patients
- No HPV testing

Chapter 4

RESULTS

4.1 Introduction

The association between HIV status and palatine tonsil cancer status is examined using cross-tabulation, and the statistical significance of the association will be tested using the chi-square test of independence. A chi-square test of independence is applied to the values obtained. Furthermore, a multinomial regression (logistic regression) is carried out to explain the same relationship, using the odds ratio. Success is represented by malignant lesions and failure by a benign lesion. A benign tumour is defined as a tumour that does not invade adjacent tissue, while a malignant tumour is defined as a tumour that invades and causes destruction of surrounding tissues.[29]

All the statistical tests were carried out with a 5% significance level. One of the conditions of the use of the chi square test is that, expected frequency count for each cell in the contingency table, must be at least 5.

All the analyses were carried out using the Statistical Packages for Social Sciences version 13 and with the assistance of Matondo Lusembo, a statistician.

4.2 Ages Of Patients

Table 4.1: Descriptive statistics of age

	Count	Minimum	Maximum	Median	Mean	Standard Deviation
Age	319	18	77	33	34.98	11.99

The ages of patients in the study range from 18 to 77 years old, with a mean age of 35 years and a standard deviation of 12 years as presented above.

4.3 Population Distribution Per Hospital

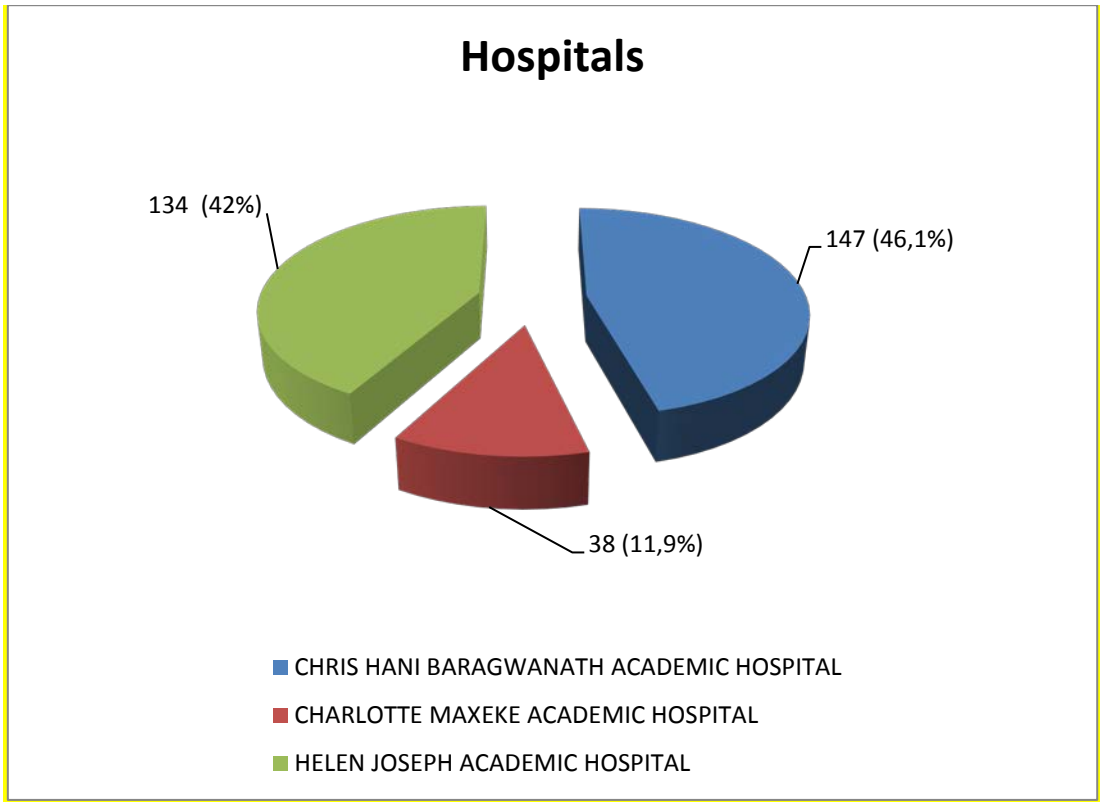

Figure 4.1 Distribution of hospital patients from each facility in this study

The Data collected indicates that 46% of patients in the study are from CHBAH, 42% from HJH and only 12% from the CMJAH.

4.4 HIV Results

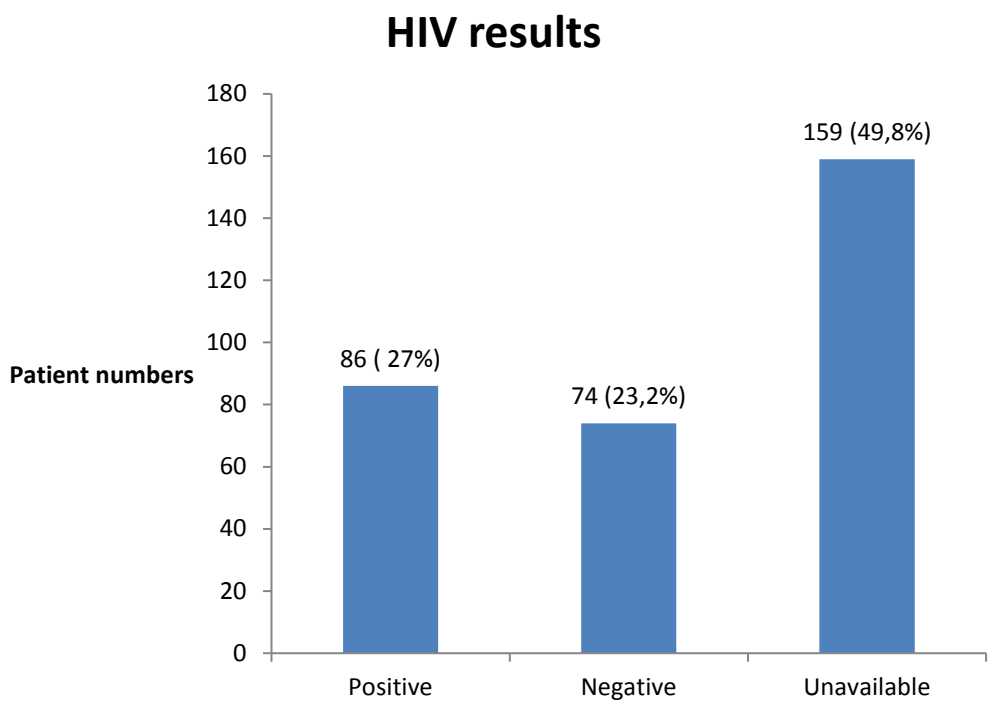

Figure 4.2 Distribution of the HIV results

The results of HIV test are presented in Figure 4.2. Half of the patients did not have HIV test results available. The majority (54%) of patients, for whom HIV results were available, had underlying HIV infection.

4.5 HIV Results Per Hospital

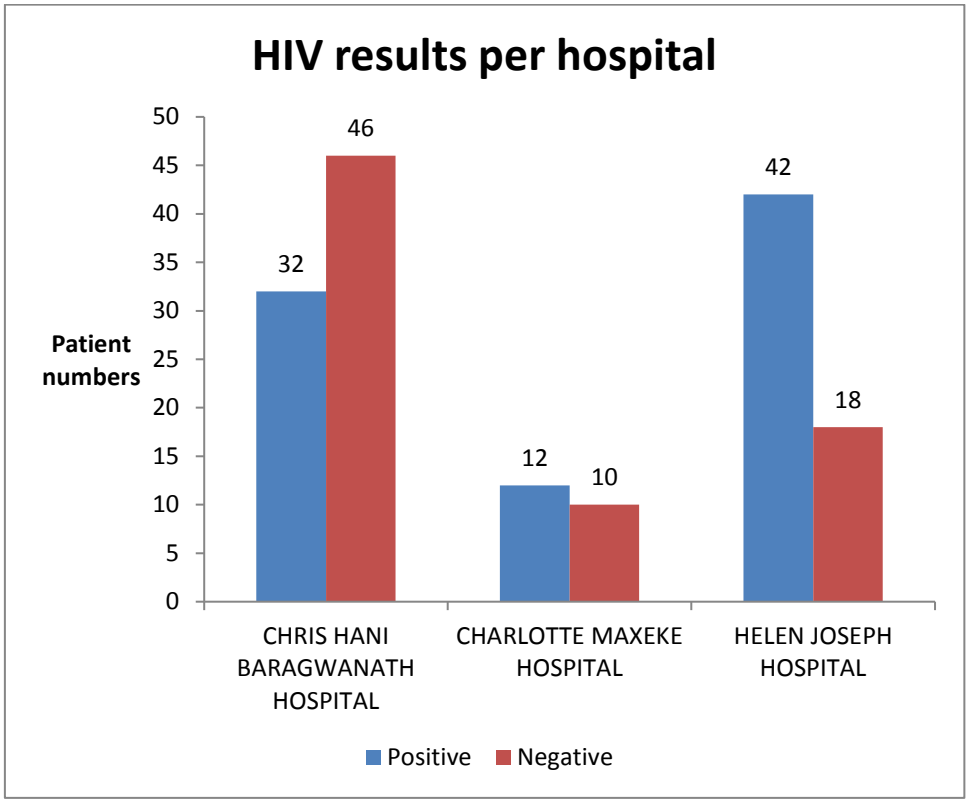

Figure 4.3 Distribution of HIV results per hospital

HJH had the highest percentage (approximately 70%) of HIV positive patients followed by CMJAH and CHBAH, with 55% and 41 % respectively.

4.6 Histology Results In All Patients

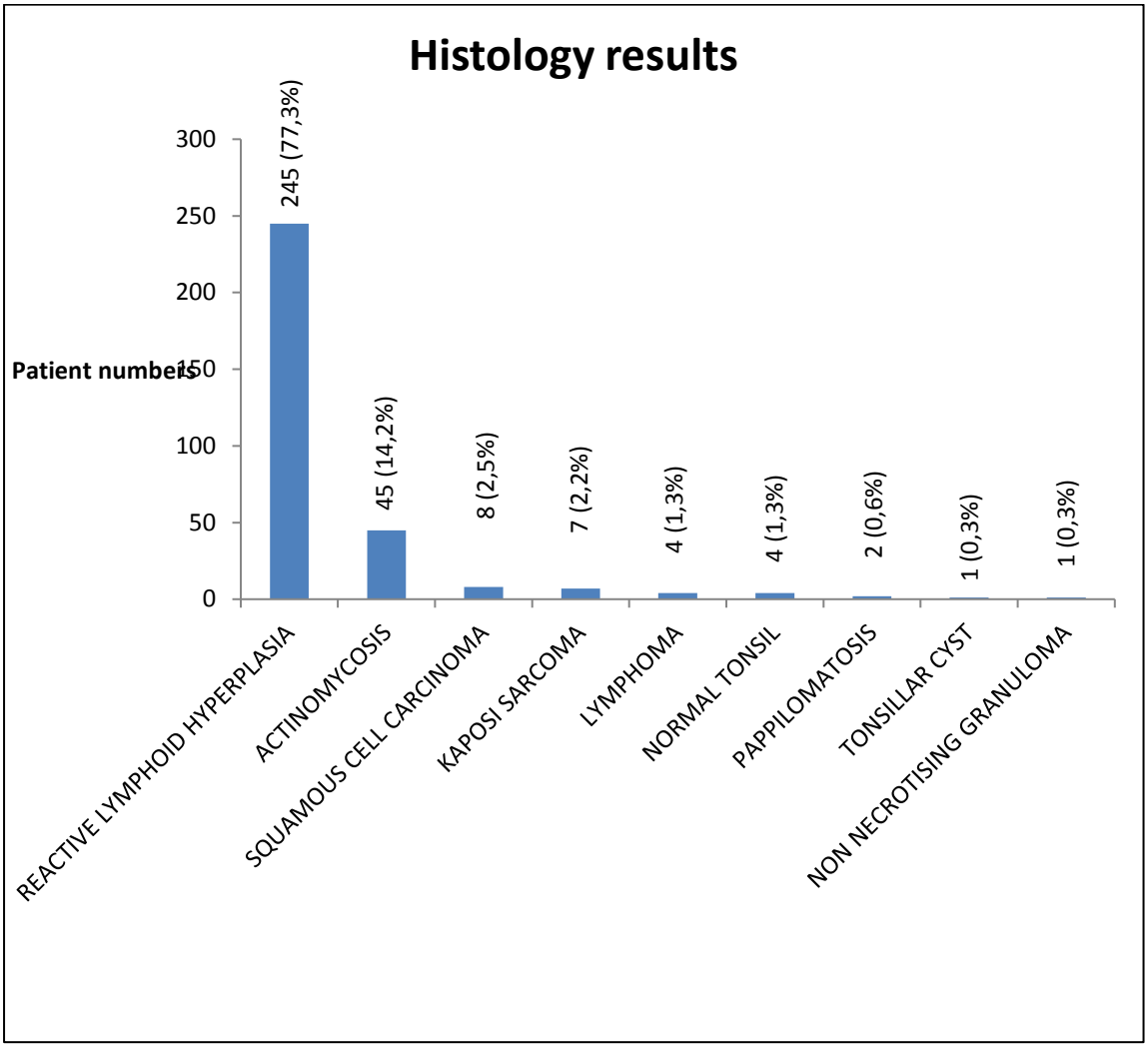

Figure 4.4 Histology Results in all patients

The tonsil histopathology test results of patients reveal that reactive lymphoid hyperplasia was the most (77%) common pathology encountered amongst our patients. This was followed by actinomycosis infection which was documented in 14% of patients.

4.7 Histology Results In HIV Infected Patients

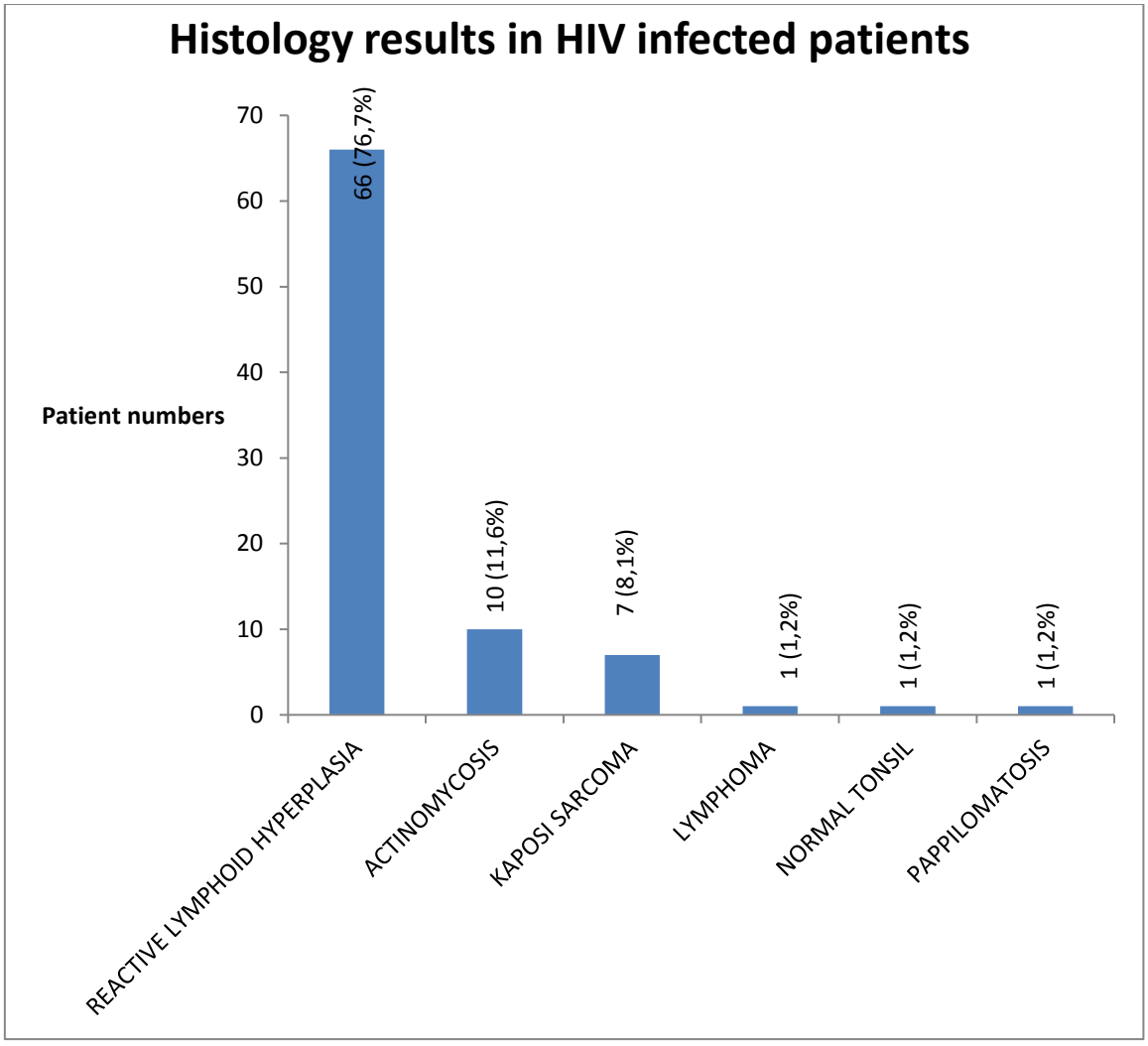

Figure 4.5: Histology results among the HIV Infected Patients

Figure 4.5 above and Figure 4.6 below indicate the distribution of tonsillar histopathology results in HIV infected and uninfected patients respectively. In both groups, reactive lymphoid hyperplasia was found in 77% of patients. Actinomycosis was found in 12% of patients in the HIV infected group while in the HIV uninfected patients it was observed in 11%.

4.8 Histology Results In HIV Uninfected Patients

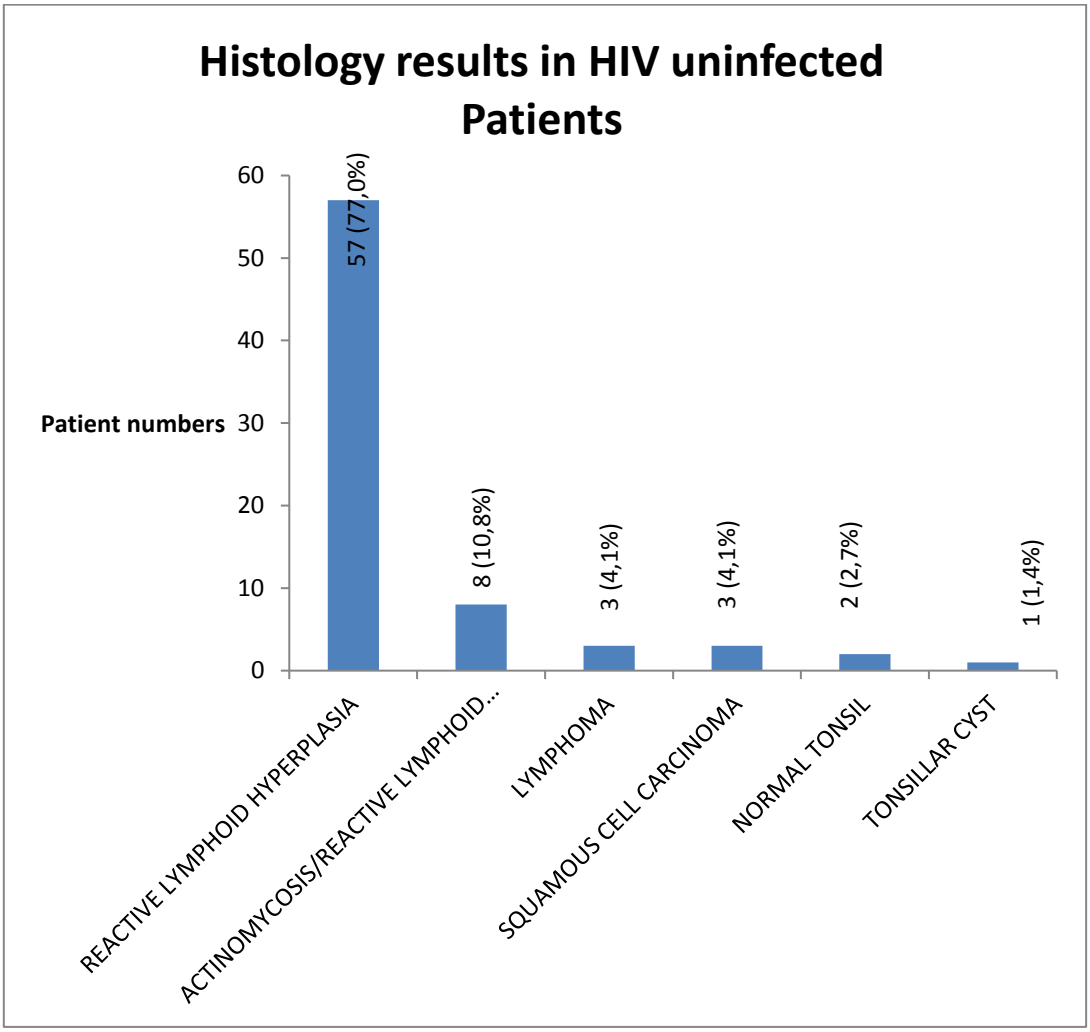

Figure 4.6 Histology results among the HIV uninfected patients.

4.9 Distribution Of Malignant And Benign Lesions

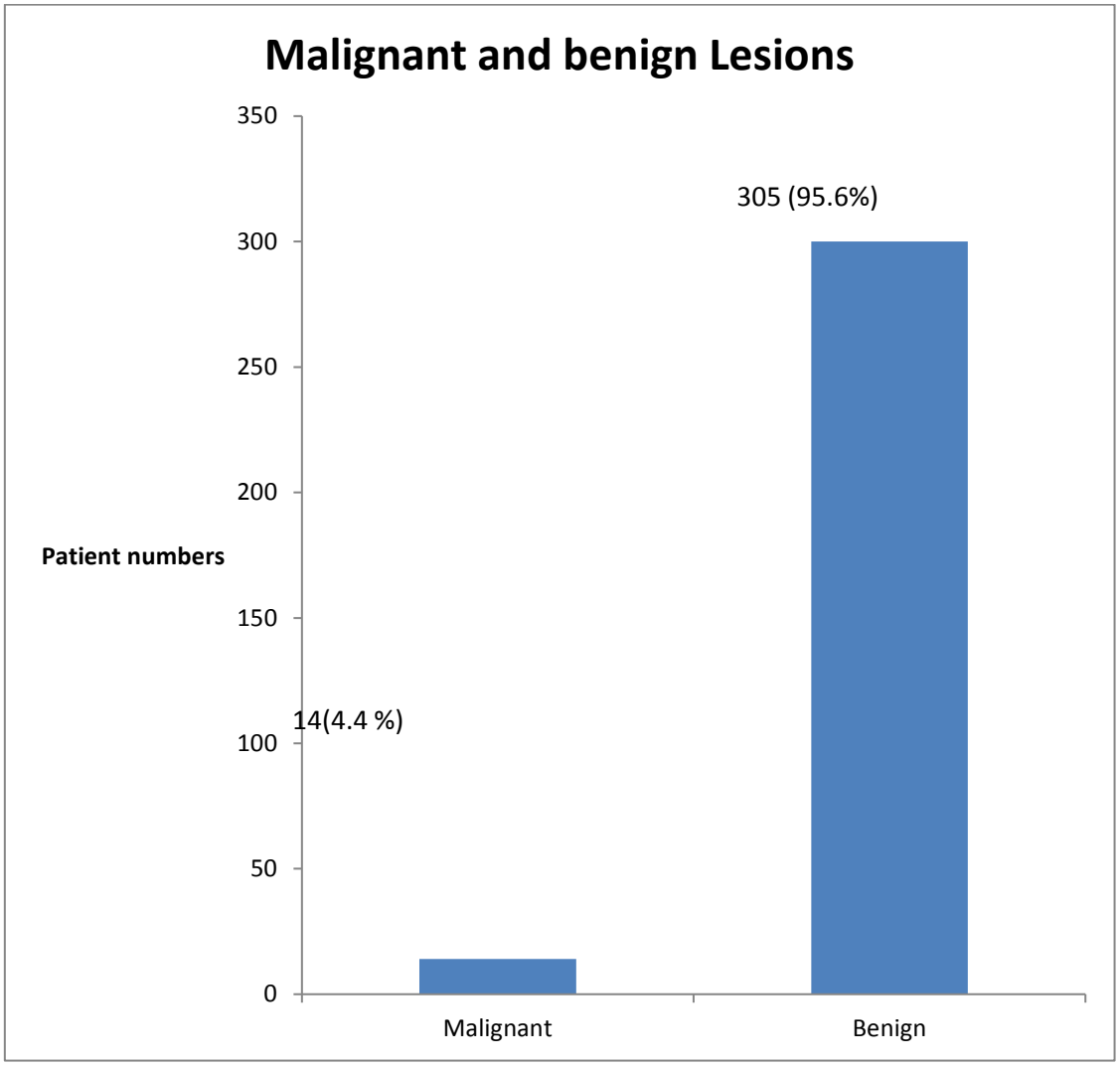

Figure 4.7 Distribution of Malignant and benign lesions

It can be seen that 95.6% of the specimens had benign lesions while in 4.4% the lesions were malignant.

4.10 Chi Square Test Of Independence

In this section, the association between malignancy and the HIV results are presented. See Table 4.2 below.

Table 4.2 The association between Malignancy and HIV status

	HIV Results		Total
	Positive	Negative	
Malignant	8	6	14
Benign	78	68	146
Total	86	74	160
Chi Square Statistic= 0,071; P-value= 0,790			

Among the 160 patients whose HIV test results are known, 86 (53.8%) are HIV infected and 74 (46.2%) are HIV uninfected. The majority of patients (both HIV positive and negative) had benign pathology of their tonsils. In the HIV infected patients, 8 patients (9.3%) had a malignant pathology. Six patients (8.1%) had malignant pathology in the HIV uninfected group.

To test whether the malignant pathology was independent of HIV disease, the chi-square test of independence was carried out. In this test, the null hypothesis (H0) was that the malignant pathology is independent of HIV disease and the alternative hypothesis (H1) is that they are dependent. As the p-value is 0.790 greater than 0.05 (5%), we fail to reject H0, at 5% significance level.

We concluded that there is no statistical evidence at 5% significance level, that the malignant pathology is related to HIV.

4.11 Logistic Regression

To predict the likelihood of having malignant tonsillar pathology in the presence of HIV infection, logistic regression was carried out. The result of the logistic regression of the malignant pathology result based on HIV results and age is presented in Tables 4.3 and 4.4 below.

Note that, the Odds ratio values in Table 4.4 are actually the adjusted Odds ratio, which is reported when multiple independent variables are used in the model. It indicates the contribution of a particular predictor when other predictors are controlled. That is for HIV results, the Odds ratio indicates the contribution of HIV infection while controlling or adjusting for age.

Table 4.3 Codification of categorical variables in logistic regression

Dependent variable encoding			
Original value		Internal value	
Benign		0	
Malignant		1	
Categorical independent variable codings			
		Frequency	Codings
			(1)
	Negative	74	0
	Positive	86	1

Table 4.3 above shows the coding of categorical variables. The first one is the dependent variable i.e. the malignant pathology and the second one is the independent variable i.e the HIV result.

For the dependent variable:

- 1 is used as the event occurring (Malignant)
- 0 as the absence of event (Benign).

For the independent variable (HIV result):

- 1 is used for the HIV positive category
- 0 for the category of reference or control group (HIV negative)

Table 4.4 Logistic regression of Malignancy at age and HIV results

Variable	Coefficient	Wald statistic	Significance	Odds ratio
Age	-0,05	5,66	0,02	0,95
HIV-Result (Positive)	0,32	0,30	0,59	1,38
Constant	4,26	19,73	0,00	71,11

The logistic regression was performed to test the effects of age and HIV infection on the presence of malignant lesions. The results indicated that when controlling the effect of age in the model, HIV infected patients are 1.380 times more likely to have malignant tonsillar pathology than the HIV uninfected patients. The Wald tests showed that only age significantly predicted the presence of malignant pathology (p-value= 0.017). HIV did not significantly predict the presence of the malignant pathology (p-value = 0.586). This result is in accordance with the chi square test in Table 4.2.

4.12 Effect Of CD4 Count On Malignant Lesions

Table 4.5 CD4 count

	Count	Minimum	Maximum	Median	Mean	Standard Deviation
CD4 Count (cells/mm^3)	107	6,00	1439,10	369,00	431.17	327.03

The CD4 counts encompass a wide range as evidenced by the value of this standard deviation.

Table 4.6 Comparison between CD4 count below 200 and malignant lesions

	CD4 Count (cells/mm^3)		Total
	<=200	>200	
Malignant Lesion	2	5	7
Benign Lesion	27	73	100
Total	29	78	107
Chi Square = 0,008; P-value= 0,928			

Patients with a lower CD4 count (below 200 cells/mm^3), would be expected to have more severe HIV disease and therefore a greater chance of having an HIV associated malignancy. In our study, a low CD4 count does not appear to affect the occurrence of malignant lesions. (p-value 0.928).

Summary of significant results

- Benign lesions (benign lymphoid hyperplasia) was most common in all patients (HIV infected and uninfected)
- Advancing age was the only predictor of malignancy
- HIV status did not result in increased overall malignancy
- Half of the patients undergoing tonsillectomy had HIV results available; and of this sub-group approximately 50% had underlying HIV infection
- No association between CD4 count and occurrence of malignancy
- All patients with KS had underlying HIV infection

Chapter 5

DISCUSSION

5.1 Benign Lesions

Table 5.1 Comparison of benign histology results

Authors	No. of Patients	Age Group (Years)	Reactive lymphoid hyperplasia (%)	Reactive lymphoid hyperplasia with Actinomycosis identified (%)	Tonsillar cyst(%)	Granuloma (%)	TB (%)	Papilloma (%)
Ikram et al[30]	200	4-49	99.5					
Younis et al[31]	339	Above 18	88.7					
Lierop and Prescott[1]	344	Below 18	93.6	5.8			0,3	
Courville et al[11]	1093	Adults	Just stated as benign, no further detail on benign lesions					
Randel et al[15]	54,901	All ages	Just stated as benign, no further detail on benign lesions					
Dell'Aringa et al[32]	250	2-34	97	0.8	0.8	0.,4		
Our study	319	18-77	77.3	14.2	0.3	0.3	0	0.6

We reviewed 319 tonsillectomy specimens. The most common finding on histopathology was reactive lymphoid hyperplasia which is an inflammatory reaction, mainly due to infection but can also be due to chemical irritation or allergies.[4] This was present in 245 (77.3%) patients. The findings were equivalent in both the HIV infected and HIV uninfected groups.

Our findings are consistent with previously published studies which found reactive lymphoid hyperplasia in the vast majority of patients (see table 5.1 above). Ikram et al reviewed 400 tonsillectomy specimens. Their patients were aged between 4-49 years. In their cohort 273 (99%) patients had reactive lymphoid hyperplasia.[30] Younis et al[31] reviewed the histopathology reports of 339 adult tonsillectomy specimens. Reactive lymphoid hyperplasia was identified in 299 (88.7%) patients.[31]

There is minimal data available on the histopathology of routine tonsillar specimens in the adult HIV infected population. A South African Study, by Lierop et al, reviewed the tonsil histology in 344 paediatric patients.[1] Reactive lymphoid hyperplasia was present in all the patients with HIV infection (4 patients). Our findings suggest that reactive lymphoid hyperplasia remains the most common finding in patients undergoing tonsillectomy, regardless of HIV status or age.

Dell'Aringa et al studied 250 patients between the ages of 2 and 34. Of these 245 (95%) had lymphoid hyperplasia or inflammation; 2 (0, 8%) had tonsillar cysts and 2 (0,8%) had actinomycosis infection. In our study which was of a similar size the population was older. There were greater proportions of patients with Actinomycosis 45 (14%); SCC 8 (2.5);KS 7 (2.2%) and lymphoma 4 (1.3%). In both studies granulomatous disease was present in only one patient.[32]

Actinomyces are commonly found in the oral cavity where they are commensals. Their role in the development of tonsillar disease has not been firmly established.[25, 26] In our study actinomycosis was equally present in both patients with (11.6%) and without HIV (10.8%). The presence of actinomycosis infection in tonsillectomy specimens is well described. Rebechi et al evaluated the routine histopathology of 281 patients who underwent tonsillectomy, most of whom had recurrent bouts of infection. They found evidence of chronic tonsillitis with colonies of actinomyces in 9.6% of their patients.[33] In view of our findings we concur with Hasan et al who suggested that actinomycosis is likely to have a causal association with recurrent tonsillitis and tonsillar hypertrophy.[34]

South Africa has one of the highest burdens of TB in the world, with an estimated 450 000 active cases in 2013.[35] We however did not detect any evidence of TB in the specimens that we reviewed. This is not unexpected as tonsillar involvement in TB infection is rare. Ricciardello et al looked at otorhinolaryngology-related TB in 304 patients. Their study was conducted in Naples. They found tonsillar involvement in only 2 patients.[36]

5.2 Malignant Lesions

SCC is the most common malignancy in patients with non-benign tonsillar lesions. It accounts for up to 7% of malignancies. Courville et al[11] tested 1093 adult patients. Of, these 75 (7%) had SCC.[11] Malignancies were suspected prior to the confirmatory histology in all of their patients. Eight of our patients (2.5%) had SCC on pathological evaluation. The HIV results were only available for 4 patients; three were uninfected and 1 patient had associated HIV infection. Randel et al found 22 patients with SCC (0.04%). They reviewed 54 901 tonsillectomy specimens. The relatively low overall prevalence in their study is probably due to the high number of paediatric tonsillectomy specimens (96%). In their adult population SCC was present in 25 patients (1.2%).[15]

Lymphomatous lesions are well described in patients with tonsillar malignancy. Their occurrence ranges from 0% to 1.74%.[1, 11, 15, 30-32] Ikram et al studied 200 patients between the ages of 4 to 49. They detected lymphoma in only one patient (0.5%).[30] Younis et al evaluated the routine histopathology in 2438 specimens. Their cohort was mainly children (2099). In the 339 adult specimens they reviewed they detected lymphoma in 6 patients (1.74%). All their lymphoma patients had suspicious clinical findings pre-operatively. We had 4 patients (1.3%) with lymphoma; one of these patients had concomitant HIV infection.

In our study advancing age was the only predictor of malignancy.

5.3 HIV Testing

The estimated prevalence rate of HIV is approximately 12.7%. This is about 7.03 million of the estimated South African population, with the highest prevalence of 18% in the age group 15-49years.[37] In half of our patients HIV results were unavailable. In the patients in whom the HIV status was known; approximately half were infected. These findings suggest that more vigorous testing is required for those adults admitted for tonsillectomies and tonsillitis.

5.4 Malignant Lesions And HIV

The relationship between tonsillar malignancies and underlying HIV is not well established. We found 14 patients with malignancies, of those 8 were HIV infected and 6 were HIV uninfected. The results showed no significant correlation between tonsil malignancy and HIV infection.

HIV infection is associated with an increased risk of a range of cancers, including KS, NHL and cervical cancer, which are considered virus-related and AIDS-defining diseases. The spectrum and incidence of NADC (smoking and virus related) has also been shown to be augmented. Franzetti et al found a higher than expected incidence of tonsil carcinoma in their review of 5924 HIV infected patients.[3] Mitsuyasu reviewed the incidence of both AIDS-defining and NADC in the USA. He did not find an increased incidence of tonsillar malignancies.[28] Grulich et al performed a meta-analysis of people with HIV/AIDS (444 172 patients). They found an increased incidence of oral cavity and pharyngeal tumours. Unfortunately they did not specify whether any of their patients had tonsillar malignancies.[38] It has been hypothesised that the malignancies associated with HIV, are due to co-existing viral infection such as HPV, EBV, hepatitis B and C and HHV 8.[28, 38]

In our study KS was detected in 7 patients, all of whom were HIV infected. There is an established strong correlation between HIV and KS which has been borne out in the literature. [3, 28, 39 and 40] HIV infected individuals in Southern Africa have a higher risk of developing KS than their counterparts in Europe.[39]Prior to the HIV epidemic, the prevalence of KS was low in Africa. There has been a marked surge in the number of KS cases.

HHV8 is implicated in this resurgence of KS. The mechanism of how HHV8 causes KS is not completely understood but it is believed to be instigated by oncoprotein production and the inhibition of tumour suppressor genes.[40]AIDS-related KS is the most aggressive sub-type. It usually begins in the head and neck. This may be due to the fact that the oropharynx is the main reservoir for HHV8.[40]

Our study did not find an association between tonsil malignancies.

5.5 Relationship Between CD4 Count And Malignancy

Franzetti et al found a significant association between NADC and low nadir CD4 counts (<200cells/mm^3). They evaluated 5924 HIV infected patients over a 26 year period. They used regression models to compare the cancer risk in their HIV infected patients to age and gender-matched individuals. We could not confirm this relationship. We cannot exclude the possibility that the retrospective nature of our study, the relatively small number of events and the large deviations of CD4 counts would make our results less reliable.

Advancing age was the only predictor of malignancy in both the HIV infected and uninfected sub-groups.

5.6 Cost Vs Benefits

Hajiioannou et al showed that the cost per patient for routine histology was 50 Euros (R735). They suggested that the cost of performing routine tonsillectomy histology was not warranted due to the extremely low detection of occult malignancies[2].

The cost of tonsil histology in the public sector is approximately R200-400. This price is based on the size of the tonsil.[41] Medico-legal costs related to undetected malignancies can be exorbitant and consequently there is no standard protocol to decide whether adult specimens should be sent for histology.

5.7 Conclusion

The discussion about routine tonsillectomy histology remains controversial even though the extensive literature review has shown extremely low levels of malignancy in unsuspicious lesions.[1, 2] Proponents fear missing malignancies and detractors believe the costs seldom justify the benefits.

Tonsil histology should probably be reserved for patients with clinically suspicious lesions independent of HIV status.

Chapter 6

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Chapter 7

APPENDICES

Appendix A

R14/49 Dr Ridwaan Essa

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M151140

NAME: (Principal Investigator)	Dr Ridwaan Essa
DEPARTMENT:	Otorhinolaryngology and Head and Neck Surgery Chris Hani Baragwanath Academic Hospital Charlotte Maxeke Johannesburg Academic and Helen Joseph Hospital
PROJECT TITLE:	A Data Analysis of the Histopathology of Adult Tonsillectomies and their Associated HIV Status Performed in the Wits University Tertiary Care Hospitals from 2005 - 2015
DATE CONSIDERED:	27/11/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Shahpar Motakef
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	09/03/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B

Data Sheet

Hospital number	sex	age	Date of surgery	HIV status	CD4 count	Histology results
						Malignant or benign lesion

Link Form

Patient number	Hospital number
1	Gt.....
2	Gp.....

Appendix C

Gant Chart

	June 16	Jul 16	Aug 16	Sep 16	Oct 16	Nov 16	Dec 16	Jan 17	Feb 17	Mar 17	Apr 17	May 17
Literature review												
Ethics application												
Preparing protocol												
Protocol assessment												
Collecting data												
Data analysis												
Writing up results and discussion												

Appendix D

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